

### **REMARKS**

Applicant respectfully requests entry of the amendments and remarks submitted herein. Claims 24-28 are amended, claims 1-23 and 31-38 are canceled, and claims 39-53 are added. Therefore, claims 24-30 and 39-53 are pending.

For the Examiner's convenience, it is noted that original claims 24-28 have been placed in independent form; that original claim 33 relates to claims 39-43; that original claim 35 relates to claims 44-48; and that original claim 36 relates to claims 49-53.

#### **Rejections under 35 U.S.C. § 112, Second Paragraph**

The Examiner rejected claims 1-38 under 37 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner made three statements to support this rejection. Each of the Examiner's statements is addressed below.

**The Examiner stated that claim 1 is confusing because it recites two contradictory functional limitations.** As discussed in the Background of the Invention (please see the Specification at pages 2 and 3), drugs encapsulated in current long-circulating pegylated liposomes demonstrate similar or diminished activity compared to non-encapsulated drugs due to the long elimination half-life provided by these long-circulating liposomes. As noted in the Summary of the Invention at page 3 of the Specification, one embodiment of the invention relates to encapsulating therapeutic agents in liposomes that provide an intermediate elimination half-life. This intermediate elimination half-life provides the beneficial properties of other liposome encapsulated products, without the reduction in efficacy that results from long elimination half-lives.

Thus, in one embodiment the invention provides therapeutic agents encapsulated in liposomes that provide an elimination half-life that is at least as great as the value of the free drug, but less than a recited value. Accordingly, the claims recite a lower value (at least as great as the value of the free drug) and an upper value (less than about 14 hours in a rat) that define a beneficial elimination half-life range for the encapsulated products. Accordingly, it is respectfully submitted that the claims do not recite contradictory functional limitations. Reconsideration and withdrawal of this rejection is requested.

**The Examiner stated that phosphatidylcholine is a single compound and that the meaning of "one or more phosphatidylcholine" in claim 2 is unclear.** The Examiner's attention is respectfully drawn to the Specification at page 6, lines 1-14 where a variety of phosphatidyl cholines are discussed. In light of this disclosure, it is respectfully submitted that the claims were clear as written. Additionally, claim 2 has been canceled, so this rejection is moot.

**The Examiner stated that the ratios in claims 18-20 were confusing.** Claims 18-20 have been canceled. Accordingly, this rejection is moot.

In light of the above remarks, it is respectfully submitted that the pending claims conform with the requirements of 35 U.S.C. 112. Accordingly, withdrawal of the rejection of claims 1-38 under 35 U.S.C. 112 is requested.

Rejection under 35 U.S.C. § 102(b)

**The Examiner rejected claims 1-13, 15-23, 25, 27, 30-34 and 36-38 under 35 USC § 102(b) as being anticipated by Lopez-Berestein (5,032,404).** This rejection is respectfully traversed.

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Dillon*, 919 F.2d 688, 16 U.S.P.Q.2d 1897, 1908 (Fed. Cir. 1990) (en banc), cert. denied, 500 U.S. 904 (1991). For anticipation, there must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the art. *Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 101 (Fed. Cir. 1991). To overcome the defense of anticipation, "it is only necessary for the patentee to show some tangible difference between the invention and the prior art." *Del Mar Engineering Lab v. Physio-Tronics, Inc.*, 642 F.2d 1167, 1172, (9th Cir. 1981).

Claims 24-28 have been placed into independent format. Each claim recites a given ratio of a phosphatidyl choline and cholesterol (for example, claim 25 recites DEPC:Cholesterol in a ratio of about 2:1).

The Examiner cited Lopez-Berestein (abstract; col. 8, lines 34-66; col. 9, lines 15-47; Examples, in particular Examples 3, 15 and claims). It is respectfully submitted that Lopez-Berestein does not describe any of the liposomes that are recited in the amended claims. At column 9, lines 15-47, Lopez-Berestein generically discusses liposome components, noting that "a preferable but not limiting combination of DMPG and DMPC has been found to be a ratio of

3 to 7....” It is respectfully submitted that this broad generic discussion does not describe any formulation with enough detail to provide an anticipatory disclosure.

Additionally, it is submitted that none of the materials prepared in the Examples of Lopez-Berestein anticipate the pending claims. For the Examiner's convenience, it is noted that,

- claims 24, 39, 44, and 49 recite a liposome that comprises HSPC:Cholesterol:DSPG in a ratio of about 4:1:0.1;
- claims 25, 40, 45, and 50 recite a liposome that comprises DEPC:Cholesterol in a ratio of about 2:1;
- claims 26, 41, 46, and 51 recite a liposome that comprises DEPC:Cholesterol:DSPG in a ratio of about 2:1:0.1;
- claims 27, 42, 47, and 52 recite a liposome that comprises DOPC:Cholesterol in a ratio of about 2:1; and
- claims 28, 43, 48, and 53 recite a liposome that comprises DMPC:Cholesterol:DSPG in a ratio of about 2:1:0.1;

Accordingly, it is respectfully submitted that the instant claims are not anticipated by the disclosure of Lopez-Berestein. Accordingly, withdrawal of this rejection is respectfully requested.

**The Examiner rejected claims 1-11, 13-24, 28, 30-34 and 36-38 under 35 USC § 102(b) as being anticipated by Hersch (5,759,571).** This rejection is respectfully traversed.

As noted above, the amended claims recite certain liposomes. It is respectfully submitted that Hersch does not describe any of the liposomes recited in the instant claims. From col. 3, line 65 through col. 6, line 63, Hersch generically discusses liposomes. It is respectfully submitted that none of this discussion describes any of the liposomes recited in the instant claims sufficiently to anticipate the claims. Additionally, the liposomes prepared in the Examples of Hersch do not anticipate any of the pending claims. Accordingly, it is respectfully submitted that the instant claims are not anticipated by the disclosure of Hersch. Withdrawal of this rejection is respectfully requested.

**The Examiner rejected claims 1-11, 13, 15-23, 31-35 and 37-38 under 35 USC § 102(b) as being anticipated by Newman (Cancer Chemother Pharmacol., 1999).** This rejection is respectfully traversed.

As a preliminary note, claims 24-28 and 36 (now claims 24-28 and 49-53) were not included in this rejection.

The SPI-077 liposomes prepared and tested in Newman are discussed at page 2 of the Specification. These pegylated liposomes have long half-lives and provide lower efficacy in human testing than free drug. Additionally, these liposomes differ significantly in composition from the liposomes recited in claims 44-48. It is respectfully that Hersch does not describe any of the liposomes recited in claims 44-48. Thus, the instant claims are not anticipated by the disclosure of Hersch. Withdrawal of this rejection is respectfully requested.

**The Examiner rejected claims 1-24, 29-35 and 37-38 under 35 USC § 102(b) as being anticipated by Abra (5,945,122).** This rejection is respectfully traversed.

Abra, from column 9 through column 13, discusses several mPEG-DSPE containing liposomes that differ significantly in structure from the liposomes recited in claims 24 and 39-43. Abra also discusses some "comparative liposomes" (see column 11, lines 33-34) that differ in structure from the liposomes recited in claims 24 and 39-43. In the Examples section, Abra prepares some mPEG-DSPE containing liposomes and some comparative liposomes that differ significantly in structure from the liposomes recited in claims 24 and 39-43. It is respectfully submitted that all of the liposomes discussed in Abra differ significantly in structure from the liposomes recited in the instant claims. Accordingly, it is respectfully submitted that Abra does not anticipate the instant claims. Withdrawal of this rejection is appropriate and is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

**The Examiner has rejected claims 4-8, 14, 18-20, 24-30, and 35 under 35 USC § 103(a) as being unpatentable over Lopez-Berestein.** This rejection is respectfully traversed.

As discussed in the Background section of the Specification, there is a need for liposomal formulations that are generally useful for improving the therapeutic index and the activity of therapeutic agents (please see page 3, lines 12-15). Applicant has discovered liposomes that provide intermediate drug elimination half-lives. These liposomes are useful for improving the therapeutic index and/or the activity of lipophilic therapeutic agents (see page 3, lines 26-28).

These liposomes also overcome some of the problems associated with previous long-circulating liposomes.

At pages 15 and 16 of the specification, data is provided for several formulations that possess the desired intermediate elimination half-lives. The instant claims recite several of the intermediate release liposome formulations tested at page 15. Additional data demonstrating the useful properties of the claimed formulations is provided at pages 16-18 of the specification and in the accompanying Figures.

In order to make a rejection under 35 U.S.C. 103(a) the Examiner first must establish a *prima facie* case of obviousness. Three criteria must be met: 1) there must be some suggestion or motivation, either in the reference or in the knowledge generally available to one of ordinary skill in the art, to modify the reference; 2) there must be a reasonable expectation of success; and 3) the prior art reference must teach all the claim limitations. M.P.E.P. 2142.

As discussed above in the rejection under 35 U.S.C. 102 over Lopez-Bernstein, the cited Lopez-Bernstein document does not describe any of the liposomes recited in the instant claims. Accordingly, the cited document does not teach all the elements of the instant claims. As a result, it is respectfully submitted that the instant claims are not *prima facie* obvious over Lopez-Bernstein. Withdrawal of the rejection is appropriate and is respectfully requested.

Additionally, at pages 15-18 of the specification, Applicant provides data that demonstrates that the liposome compositions recited in the instant claims provide liposomes having beneficial elimination half-lives as well as useful therapeutic properties. Accordingly, the specification provides data showing that the recited claim elements relating to the composition of the liposomes provide materials having useful properties.

**The Examiner has also rejected claims 4-8, 14, 18-20, 24-30, and 35 under 35 USC § 103(a) as being unpatentable over Hersch.** This rejection is respectfully traversed.

As discussed above in the rejection under 35 U.S.C. 102 over Hersch, the cited Hersch document does not describe any of the liposomes recited in the instant claims. Accordingly, the cited document does not teach all the elements of the instant claims. As a result, it is respectfully submitted that the instant claims are not *prima facie* obvious over Hersch. Withdrawal of the rejection is appropriate and is respectfully requested.

Additionally, at pages 15-18 of the specification, Applicant provides data that demonstrates that the liposome compositions recited in the instant claims provide liposomes

having beneficial elimination half-lives as well as useful therapeutic properties. Accordingly, the specification provides data showing that the recited claim elements relating to the composition of the liposomes provide materials having useful properties.

**The Examiner has also rejected claims 2-4, 6-12, 18-20, 24-30 and 33-35 under 35 USC § 103(a) as being unpatentable over Abra.** This rejection is respectfully traversed.

As discussed above in the rejection under 35 U.S.C. 102 over Abra, the cited Abra document does not describe any of the liposomes recited in the instant claims. Accordingly, the cited document does not teach all the elements of the instant claims. As a result, it is respectfully submitted that the instant claims are not *prima facie* obvious over Abra. Withdrawal of the rejection is appropriate and is respectfully requested.

Additionally, at pages 15-18 of the specification, Applicant provides data that demonstrates that the liposome compositions recited in the instant claims provide liposomes having beneficial elimination half-lives as well as useful therapeutic properties. Accordingly, the specification provides data showing that the recited claim elements relating to the composition of the liposomes provide materials having useful properties.

For the Examiner's convenience, it is noted that the scope of claims 24-28 has not been changed by the amendments herein. Rather, the original dependent claims have been placed in independent form. Accordingly, if the Examiner introduces a new ground of rejection for claims 24-28 in a subsequent Office Action, Applicant requests that the subsequent Office Action not be made Final.

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**CONCLUSION**

The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby.

**If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.**

Respectfully submitted,

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By their Representatives,

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